

Prevalence of Narcotic Bowel Syndrome in Opioid Abusers in Iran

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ABSTRACT

BACKGROUND

In spite of the increasing trend in opioid abusers worldwide, the prevalence of narcotic bowel syndrome (NBS) is undetermined. We aimed to estimate the prevalence of NBS and other opioid bowel dysfunction (OBD) in opioid abusers in Kerman, southeast Iran. According to the best of our knowledge, this is the first study to assess the prevalence of NBS in opioid abusers.

METHODS

By referring to addiction treatment centers in Kerman city and in a cross-sectional study, 577 subjects with opium or opioid substance abuse were included in our study. A validated questionnaire was used for OBD assessment and diagnosis of NBS was made according to both the presence of chronic abdominal pain despite increasing the opioid dose and ruling out other causes of abdominal pain. SPSS software version 16 was used for data analysis. p value < 0.05 was considered as statistically significant.

RESULTS

Constipation, regurgitation, and heartburn were the most gastrointestinal complaints that were found in 132 (22.9%), 123 (21.3%) and 91 (15.8%) subjects, respectively. Only 16 (2.8%) participants fulfilled all the NBS criteria. Simultaneous use of non-narcotic sedative drugs increased the risk of NBS significantly (the odds ratio 3:1 and $p=0.049$).

CONCLUSION

NBS is not rare among opioid abusers and should be considered as a cause of chronic abdominal pain in this group.

KEYWORDS

Opioid bowel dysfunction, Narcotic bowel syndrome, Prevalence, Opioid abuser, Iran

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INTRODUCTION

Because of the effects of opiates on gastrointestinal (GI) movement, opioid bowel dysfunction (OBD) is a well known disorder in narcotic analgesics users. This disorder commonly manifests by bowel motility symptoms such as bloating, ileus, constipation, and nausea but worsening abdominal pain that is defined as narcotic bowel syndrome (NBS) also have been described.¹⁻⁴

NBS is described as constant or recurrent abdominal pain, which is

paradoxically aggravated by continuing or decreasing the doses of narcotics.⁵ As a result of having no International Classification of Disease (ICD) code and not including in the last functional GI disorders categorization, NBS has still remained as an under-recognized disorder.^{6,7} Consequently, physicians often overlook this disorder as a cause of abdominal pain leading to sparse information about its prevalence in narcotic users.⁷⁻⁹

There are a few epidemiological data about the prevalence of NBS, most of which have been derived from limited case reports and small case series.^{1,10-13} Limited studies showed that NBS was rare among patients with cancer who used narcotics as analgesics.¹⁴ The estimated prevalence of NBS is reported as 4.2–6.4% in people with constant opioid abuse¹⁵, although by increasing opioid usage as analgesics or substance abuse in the world, the burden of this syndrome may be risen.^{3,7}

In this study we aimed to determine the prevalence of NBS and other opioid bowel dysfunction symptoms in opioid abusers in Kerman city, south-east Iran. According to the best of our knowledge, up to now, no study was performed to estimate the prevalence of NBS in opioid abusers worldwide.

MATERIALS AND METHODS

Participants

In a cross-sectional study, from February to September 2013, 650 patients who referred to 5 major addiction treatment centers in Kerman city, were included by convenient and consecutive sampling method in our study. Inclusion criteria were at least 5 weeks daily opium and/or methadone and/or heroin use. Patient with past medical history of abdominal pain and/or simultaneous consumption of cocaine or its derivatives were excluded from the study.

The Talley-Bowel Disease Questionnaire (Talley-BDQ), which is an adequate validated questionnaire that developed 25 years ago, was used to determine the presence of GI symptoms including: abdominal pain, heartburn, regurgitation, nausea, vomiting, bloating, constipation, and diarrhea in the participants.^{16,17} Details of abdominal pain was

asked and the patients were defined as having NBS when all the following criteria existed^{10,15,18}:

- more than 2 weeks narcotic use
- Chronic abdominal pain (more than 1 month) in the setting of continuous or increasing dosages of narcotics
- worsens or incompletely resolving pain with continuous or increasing dosages of narcotics
- abdominal pain increase when the narcotic dose wanes
- Symptoms improvement when narcotics are re-instituted
- No other GI diseases can justify such abdominal pain

All of the above criteria and presence of other GI complaints such as chronic constipation, diarrhea, vomiting, bloating, and heart burn in addition to the demographic data were separately collected for each participant. A general practitioner supervised the selection process in each center and completed the questionnaires through direct interview.

All the subjects who were suspicious as having NBS were referred to an expert gastroenterologist to perform laboratory tests (including CBC, BUN, Cr, and serum lead level), and endoscopic and imaging studies to rule out other causes of abdominal pain.

Statistical analysis

Frequency and percentage were used for categorized qualitative variables in addition to mean and standard deviation for quantitative variables. Pearson's Chi square test and also Fisher's exact test were used to compare age and sex difference between each group. Univariate and multivariate logistic regression tests was used to assess the impact of age, gender, education, occupation, cigarette smoking, and sedative drug in the incidence of NBS. SPSS software version 16 was used for data analysis. p value < 0.05 was considered as statistically significant.

Ethics

All the Patients consented to participate in the study and the Ethical Review Committee of the

Faculty of Medicine, Kerman University of Medical Sciences approved the protocol of the study.

RESULTS

Of the 654 patients, 77 patients excluded from the study (55 had history of other substance abuse, 22 had past medical history of GI discomfort, and 10 had both history). So 577 patient were in our study.

The mean age of the participants was 38.5±5.9 years. 61.9% of the patients were lower than 40 years old. 89.9% were men. The most frequent type of abused drug was methadone (79.9%) with the mean abuse duration of 3.9±5.7 years. Nearly 13.2% of the patients reported the simultaneous use of non-narcotic sedatives. More details of demographic characteristics of the patients are presented in table 1.

Most reported digestive disorders were constipation (22.9%), regurgitation (21.3%) and heartburn (15.8%). Diarrhea and vomiting had lower frequencies. The frequency of flatulence and nausea was 10.7% and 7.3%, respectively. According to Chi square test results, women had significantly higher prevalence of heartburn ($p=0.009$), nausea ($p=0.044$), vomiting ($p=0.008$), and bloating ($p=0.001$) compared with men. Such sexual difference was not found for complaints such as diarrhea, regurgitation, and constipation.

Except for bloating, there was not statistically significant difference between the variety of digestive complaints between the two age groups (>40 versus ≤40 years old). Bloating was more prevalent in higher than 40 years old patients compared with younger patients ($p=0.01$).

Table 2 summarizes the frequency, age, and sexual distribution of functional bowel disease among the participants.

Among 94(16.3%) patient with chronic abdominal pain, only 16(2.8%) fulfilled all the NBS criteria. NBS was seen in 6.9% of women and 2.3% of men but this difference had borderline significance ($p=0.067$). There was not statically significant difference ($p=0.95$) in prevalence of NBS between the two age groups (>40 versus ≤40 years old). Table 3

Table 1: The demographic characteristics of the studied population

Variables	Mean (±SD) or Frequency (%) (N=577)
Average age (years) *	38.5±5.9
≤40	357(61.9) **
>40	220(38.1)
Sex	
Men	519 (89.9)
Women	58(10.1)
Education	
Uneducated	252(43.7)
Elementary	168(29.1)
High school or Diploma	130(22.5)
College degree	27(4.7)
Job	
Private sector	221(38.3)
Without work (unemployed - housewife - Student)	171(29.6)
Hand working (driver-worker-farmer-welder-mechanic)	124(21.5)
Government employment (employee - retired)	61(10.6)
Type of drug used	
Methadone	461(79.9)
Opium	54(9.4)
Opium syrup	9(1.6)
Opium extract	32(5.5)
Heroin	20(3.5)
The mean duration of drug abuse (years)	3.9±5.7
Alcohol drinking	5(0.9)
Cigarette smoking	365(63.3)
Average number of cigarettes consumed per day	14.5±9.5
The mean duration of smoking (years)	15.5±9.7
Non-narcotic sedative drug consumption	76(13.2)

* Mean ± Standard deviation

** (percent)

shows more details of chronic abdominal pain and NBS related symptom in the patients.

According to the results of univariate test, women was three times more susceptible to NBS with borderline statistical significance (p value=0.055) and the use of sedative drugs significantly increased the risk of NBS($p=0.039$). Other variables had no significant effect on the incidence of this syndrome ($p>0.05$).

Results of multivariate analysis (after adjusting for the confounding effect of variables on each oth-

Table 2: The frequency, age, and sexual distribution of functional bowel dysfunction among the participants

Symptom	Frequency	Sex		p value	Age		p value
		Male (n=519)	Female (n=58)		>40 (n=220)	≤40 (n=357)	
Heartburn	91(15.8)	75(14.5)	16(27.6)	0.009	39(17.7)	52(14.6)	0.31
Regurgitation	123(21.3)	106(20.4)	17(29.3)	0.11	55(25)	68(19)	0.09
Nausea	42(7.3)	34(6.6)	8(13.8)	0.044	17(7.7)	25(7)	0.74
Vomiting	19(3.3)	13(2.5)	6(10.3)	0.008	7(3.2)	12(3.4)	0.90
Bloating	62(10.7)	48(9.2)	14(24.1)	0.001	33(15)	29(8.1)	0.01
constipation	132(22.9)	115(22.2)	7(29.3)	0.21	82(23)	50(22.7)	0.94
Diarrhea	20(3.5)	16(3.1)	4(6.9)	0.13	9(4.1)	11(3.1)	0.52

Table 3: Details of chronic abdominal pain and frequency of NBS in the participants

	Frequency	Age		p value	Sex		p value
		>40 (n=220)	≤40 (n=357)		Female (n=58)	Male (n=519)	
Having abdominal pain	94(16.3)	36(16.4)	58(16.2)	0.037	15(25.9)	79(15.2)	0.97
Severe abdominal pain that interfere with daily activity	87(15.1)	30(13.6)	57(16)	0.38	11(19)	76(14.6)	0.44
No improvement in abdominal pain after increasing the dose of opium	46(8)	23(10.5)	23(6.4)	0.22	7(12.1)	39(7.5)	0.084
Pain significantly deteriorated with discontinuing the opium and partial improvement with starting opium again	55(9.5)	16(7.3)	39(10.9)	0.10	9(15.5)	46(8.9)	0.14
Progressive increase in the duration and severity of abdominal pain	23(4)	10(4.5)	13(3.6)	0.057	5(8.6)	18(3.5)	0.59
No other disease explained the abdominal pain	44(7.6)	19(8.6)	25(7)	0.41	6(10.3)	38(7.3)	0.47
Narcotic bowel syndrome (NBS)	16(2.8)	6(2.7)	10(2.8)	0.067	4(6.9)	12(2.3)	0.95

er) showed that the risk of NBS in women was approximately 1.8 more than men but this difference was not significant ($p=0.44$). Similar to the results of univariate logistic regression test, the use of sedative drugs had a significant impact on increasing the risk of this syndrome (the odds ratio 3:1 and $p=0.049$). Other variables such as occupation, education, smoking, and age had no significant effect on the incidence of NBS ($p>0.05$).

The impact of demographic factors such as age, sex, education, occupation, cigarette smoking, and using sedative drugs on the incidence of NBS by assessment with univariate and multivariate logistic regression tests is summarized in table 4.

DISCUSSION

Firstly in 1984, Sandgren and colleagues reported

chronic abdominal pain in five patients with long term abuse of narcotic analgesics that resolved after cessation of the substance.¹¹ Later in 1989, Rogers and co-workers discussed the detail of this syndrome.⁵ In 2009, the only population based study about the prevalence of NBS in narcotic analgesic users was published by Rok Seon Choung et al. According to the results of that study probable NBS was shown in only five (0.17%) of 2,913 participants.¹⁹ In another study in patients with non-cancerous, non-gastrointestinal pain, and chronic narcotic use, 6.4% of 98 participants fulfilled the criteria of NBS.¹ The Prevalence of NBS in our study was 2.8%. We found that NBS was not rare among opioid abusers. Higher prevalence of NBS in our study may be due to longer duration and higher dose of opioid consumption in the study population.

Table 4: Demographic characteristics of patients with NBS

Variables		Crude odds ratio	p value	Modified odds ratio	p value
Age (years)	≤40(Reference)	-	-	-	-
	>40	3.1(0.97-10.1)	0.055	1.8(0.38-9.1)	0.44
Sex	Man(Reference)	-	-	-	-
	Woman	0.97(0.34-2.7)	0.95	0.96(0.32-2.8)	0.94
Education	Uneducated (Reference)	-	-	-	-
	Elementary to high school	1.2(0.4-3.6)	0.76	1.2(0.35-3.8)	0.79
	Diploma or higher level	0.75(0.2-2.9)	0.68	0.74(0.17-3.1)	0.69
Job	Private sector (Reference)	-	-	-	-
	Without work (unemployed - housewife - Student)	1.8(0.57-5.9)	0.30	1.3(0.30-5.6)	0.71
	Hand working (Driver - worker- farmer...)	1.1(0.25-4.5)	0.92	1.1(0.24-4.8)	0.90
	Government employment (employee - retired)	0.72(0.1-6.2)	0.76	0.82(0.10-7.5)	0.86
Cigarette smoking		0.57(0.21-1.5)	0.27	0.65(0.21-1.9)	0.65
Non-narcotic sedative consuming		3.1(1.1-9.2)	0.039	3.1(1.1-9.3)	0.049

In our study there was not significant association between the prevalence of NBS and age, sex, education, and occupation. However, simultaneously use of sedative analgesics increase the risk of NBS significantly (the odds ratio 3:1). We think this effect may be due to the exacerbation of NBS mechanism by non-narcotic sedative analgesics but more studies are required for the assessment of the effect of sedative analgesics on GI system.

Mechanism of OBD is well recognized by suppressing of GI and biliary motility through the μ -receptors^{20,21} but pathophysiology of aggravating pain that nominated as NBS is uncovered.¹⁸ However, three mechanisms may explain the pathology of pain facilitation in prolonged opioid abusers:

1) New studies in mice showed activation of two different pathways called biomodal effect of opium on afferent neuron in dorsal horn; higher concentration of opiate inhibits neurotransmission and produces analgesia. In contrast lower concentration and prolong use, activates GS protein excitatory receptor then cause hyperalgesia and tolerance.^{18, 22-24}

2) Among specific regions of the brain that modulate afferent pain signals at the level of the spinal cord, the rostral ventral medulla (RVM) has paradoxical role on nociceptive input. These responses may be due to activation or inactivation of on and off cells in the RVM. Activation of the on and off cells cause inhibition and facilitation of nocicep-

tive input, respectively. Furthermore, dynorphin, an endogenous opiate with or without overlapping by cholecystokinin and cholecystokinin receptors in the central nervous system enhance pain transmission in these descending pathways.^{18,25,26}

3) Injury, inflammation, or infection and some drugs such as morphine activated dorsal horn glia (astrocytes and microglia). These cells have various receptors for neurotransmitters and neuromodulators and produce proinflammatory cytokines such as tumor necrosis factor, interleukin-1, and interleukin-6 that all of them facilitate pain pathway at central nervous system.^{15,18,27,28}

The strengths of this study was that diagnosis of NBS was not limited only to questionnaire and all patients with abdominal pain was referred to an expert gastroenterologist to rule out other causes of abdominal pain such as irritable bowel syndrome and lead poisoning by laboratory and imaging studies.

The important limitation of our study was that the studied populations were opioid abusers who were referred to addiction treatment centers and some of these patients may decide to treatment for some complication such as OBD, so we may overestimate the prevalence of NBS. As a consequence, we suggest a population based study for assessment of the prevalence of NBS in opioid abusers.

In conclusion, in our survey, contrary to previous studies NBS is not rare among opioid abusers and

should be considered as a cause of abdominal pain in this population.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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